PROPUESTA

PROYECTO FIN DE CARRERA

"Use of analysis of variance in Veterinary Medicine "

Departamento de Estadistica

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Chapter 1

Introduction

The main purpose of the Final Project is to show how to conduct one veterinary experiment. It can be divided into three phrases: planning, implementation, analysis. These three phrases should be complementary from the begining to the end of the veterinary experiment. During the planning is important to set goals that will be pursued and the instruments that will be used.

During the implementation of the experiment the most important thing is the selection of the units and the methods that are used.

After passing these two phrases comes the last phrase analysis of the data. This stage includes various statistical procedures, analysis and methods so we can make conclusion and summaries, and describe the characteristics.

The main problem in this Final Project is to study the effect of two medicaments on a particular population and to compare the effects they produce on treated experimental units.

In the Final Project we will keep the requirements listed in “Guideline on Statistical Principles for veterinary clinical trials”.

We will use the software package Statistica to make the conclusions in the end of the Final Project.

Chapter 2
Guideline on Statistical Principles for Veterinary Clinical Trials

The focus of this guideline is on statistical principles. In this guideline the role of statistics in clinical trial design and analysis is acknowledged as essential. The guideline is written primarily to harmonise the principles of statistical methodology applied to clinical trials. The guideline is intended to give directions to sponsors in the design, conduct, analysis and evaluation of clinical trials of an investigational veterinary product in the context of its overall clinical development.

2.1 Considerations for Overall Clinical Development

The broad aim of the process of clinical development of a veterinary medicinal product is to determine whether there is a dose at which the product can be shown to be simultaneously safe and effective. Satisfying these broad aims usually requires an ordered programme of clinical trials, each with its own specific objectives. This should be specified in an ordered development plan, with appropriate decisions points and flexibility to allow modification as knowledge accumulates.

Depending on the aim of the trial, it can be classed in one of the following three categories: confirmatory, exploratory, or composite.

2.2 Type of Clinical Trials

2.2.1 Confirmatory trial

Confirmatory trials can concern dose determination trials, dose confirmation trials as well as controlled field trials.

Confirmatory trials :

- Are controlled.
- Have an agreed protocol written and signed before the study begins.
- Test a hypothesis that is started in advance.
- Only address a limited number of questions.
- Are necessary to provide firm evidence of efficacy and/or in-use safety.
- Estimate with due precision the size of the effects attributable to the treatment under evaluation and relates these effects to their clinical significance.
- Are justified in terms of their design and other statistical aspects such as planned analysis.
- Clearly and definitively answer each question relevant to support the started hypothesis.
- Explain the generalisation from the chosen study animal population.
- Produce robust results.

2.2.2 **Exploratory Trial**

The rationale and design of confirmatory trials often rests on earlier clinical work carried out in a series of exploratory studies. Exploratory trials are:

- Precursors to confirmatory trials.
- Also have clear objectives.
- Such objectives may not always lead to simple tests of predefined hypotheses.
- Sometimes require data exploration during analysis.
- The choice of the hypothesis may be data dependant.

2.2.3 Composite trial

It may have both confirmatory and exploratory aspects.
The protocol should make a clear distinction between those aspects of the trial which are confirmatory and those which are exploratory.

2.3 Population

In the earlier phases of new product development the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence. They may come from a very narrow sub-group of the total animal patient population for which the product may eventually be indicated. No individual clinical trial can be expected to be totally representative of the future target population because of potential influences of, for example, geographical location, timing, animal husbandry, and local veterinary clinical practices. Wherever possible the influence of such confounding factors should be taken into account and subsequently discussed during the interpretation of the trial results.

2.4 Primary and Secondary Variables

2.4.1 Primary Variable

The primary variable should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. Generally there should only be one primary variable.
The variable should be reliable and validated and derived from experience in previous studies or in published scientific literature. These should be sufficient evidence that the chosen primary variable can provide a valid and reliable measure of some clinically relevant and important clinical benefit in the study animal population as defined by the

inclusion and the inclusion criteria. This is generally variable used to estimate the sample size.

2.4.2 Secondary Variables

Secondary Variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. Their pre-definitions in the protocol is also important.

In some situation it may be useful to combine the multiple measurements into a single or "composite" variable using the pre-defined algorithm. The method of combining the multiple measurements should be specified in the protocol. Combining multiple measurements addresses the multiplicity problem without requiring adjustment for multiple comparisons.

2.5 Design Techniques to Avoid Bias

Other sources of bias arise during the conduct and analysis of a clinical trial. The two most important design techniques for avoiding bias in clinical trials are blinding and randomisation.

2.5.1 Blinding

Blinding is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial which may arise from the knowledge of specific treatment a study animal may be receiving or is about to receive. The essential aim is to prevent identification of the treatment until all such opportunities for bias have passed. Therefore is important to try achieving optimum blinding (full-blinded story).

A full-blinded trial is one in which the investigator and sponsor stuff involved in the treatment or clinical evaluation, the owner or carers of the study animals, or any other

persons associated with administrating the treatment are unaware of the treatment received by the study animals.

2.5.2 Randomisation

It also tends to produce treatment groups in which the distributions of prognostic factors (known and unknown) are similar. The randomisation schedule of a clinical trial documents the random allocation of treatments to study animals.

2.6 Study Design Considerations

2.6.1 Parallel Group Design

The most common clinical trial design for confirmatory trials is the parallel group design in which study animal are randomised to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and generally one or more control treatment, such as placebo and/or an active comparator.

2.6.2 Cross-over design

In the cross-over design, each study animal is randomised to a sequence of two or more treatments, and hence acts as its own control for treatment comparisons. The most common use of cross-over design is to demonstrate the bioequivalence.

2.6.3 Factorial Designs

In a factorial design two or more treatments are evaluated simultaneously in the same set of subjects through the use of varying combinations of the treatments. The simplest examples is the 2x2 factorial design in which study animals are randomly allocated to one of the four possible combinations of two treatments, A and B say. These are: A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B. The statistical test of interaction is model dependent and may lack power to detect an interaction if the sample size was calculated based on the test for main effects.

2.7 Type of comparison

All the studies should be designed to control the risk of concluding erroneously what they are supposed to demonstrate.

2.7.1 Show Superiority

Superiority studies are designed to detect a difference. Scientifically, efficacy is more convincingly established by demonstrating superiority to an active control treatment or by demonstrating a dose response relationship.

2.7.2 Trials to show Equivalence or Non-inferiority

Active control equivalence or non-inferiority trials may also incorporate a placebo, thus pursuing multiple goals in one trial, for example, establishing superiority to placebo and

hence validating the study design and evaluating the study design and evaluating the degree of similarity of efficacy and safety to the active comparator.

2.7.3 Dose-response Designs

Dose response studies may serve a number of objectives, amongst which the following are of particular importance:
The confirmation of efficacy: the investigation of the shape and location of the dose-response curve; the estimation of an appropriate starting dose; the identification of optimal strategies for individual dose adjustments; and/or the determination of a maximal dose beyond which additional benefit would be unlikely to accur.

2.7 Interim Analysis and Early Stopping

The goal of such an interim analysis is to stop the trial early if the superiority of the treatment under study is clearly established. If the demonstration of a relevant treatment difference has become unlikely or if unacceptable adverse effects are apparent.

2.8 Data Analysis

- Definition of the experimental unit.
- Hypothesis to be tested.
- Treatment effect(s) to be estimated.
- Statistical model. Test(s) and constructions of confidence intervals.
- Justification of the use of one- or two-sided tests.

- Use of covariate(s).
- Significance threshold.
- Power (1-β) and other assumptions used in sample size estimation.
- Set of experimental units to be included in the analysis.
- Planned data transformations.
- Bayesian estimates.
- Reporting of summary data.
- Comparison of groups at baseline.
- Alternative methods to be used in case of expected problems

3. Analysis of Variance

Analysis of variance can be viewed as a special case of multiple regression where the explanatory variables are entirely qualitative.

3.1 One-way analysis of Variance

One way analysis of variance can be viewed as a special case of bivariate analysis.The two variables X and Y, whose relationship is to be studied, represent a qualitative variable Y and a quantitative variable X. The variable Y is assumed to be a continuous random variable with density f(Y). The variable X is assumed to be a classification variable with g categories. The interrelationship between the two variables therefore involves a comparison of distribution of Y among the g categories of X. Such analyses may involve comparison of distribution parameters such as means or variances or may involve direct comparison of the density functions. The procedures that involve a comparison of the means have traditionally been referred to as analysis of variance.

The term analysis of variance was first applied to these procedures because the statistical tests involve comparisons of various sums of squares or variation. The classification

variable X is usually referred to as a factor and the categories of X are called levels. The one-way analysis of variance is also called a single factor analysis of variance.

Many scientific studies include the comparison of the properties of items which have been classified into types of brands or categories. Examples of such categories include varieties of an agricultural product such as corn, various brands of a consumer good such as soap and various methods of carrying out a task such as treating a patient or advertising a product.

3.1.1 The Sampling Model

One column of the data matrix contains observations on a continuous random variable Y. A second column of the data matrix contains observations on a classifications variable X which classifies the n individuals or objects into g categories or groups. The X variable assumes one of the g integer values 1, 2, 3,…,g. We can view the n individuals as a random sample from a populations which after classification according to X resulted in totals of $n_1, n_2, ..., n_g$ observations from the g groups respectively.

The means for the distributions of Y for the g groups are denoted by $\mu_1, \mu_2, ..., \mu_g$, while the variances are assumed to be homogeneous with magnitude σ^2.The distribution of Y is assumed to be normal for each group.

The model describing the behaviour of the Y observations may be written as:

$$y_{ij} = \mu_j + \varepsilon_{ij}, \qquad i = \overline{1, n_j};\ j = \overline{1, g}$$

$$\varepsilon_{ij} \in N(0, \sigma^2)$$

Where ε_{ij} represents a random variable with mean 0 and variance σ^2. By assumption the ε_{ij} are mutually independent. This model is sometimes called a cell means model. Under the assumption of homogeneity of variance the best unbiased estimator of μ_j is $\overline{y_{.j}}$.The model therefore can be written:

$$y_{ij} = \overline{y}_{.j} + (y_{ij} - \overline{y_{.j}}) \qquad i = 1, 2, ..., n_j \qquad j = 1, 2, ..., g$$

With $\overline{y_{.j}}$ as an estimator of μ_j and $(y_{ij} - \overline{y_{.j}}) = e_{ij}$ as an estimator of ε_{ij} .The predicted values for y_{ij} from this model are $\hat{y}_{ij} = \overline{y_{.j}}$.

Sums of Squares

The total variation in Y over the sample, SST or the total sum of the squares,is described by:

$$SST = \sum_{j=1}^{g} \sum_{i=1}^{n_j} (y_{ij} - \overline{y_{..}})^2$$

The Total Sum of Squares measures the variation in the Y values around the grand mean or overall mean given by

$$\overline{y_{..}} = \sum_{j=1}^{g} \sum_{i=1}^{n_j} \frac{y_{ij}}{n_j} \qquad \text{where } n = \sum_{n=1}^{g} n_j$$

The variation explained by the fitted model is given by SSA, the sum of squares among groups. This Sum of Squares Among Groups measures the variation among the group means and is determined as:

$$SSA = \sum_{j=1}^{g} \sum_{i=1}^{n_j} (\hat{y}_{ij} - \overline{y_{..}})^2 = \sum_{j=1}^{g} \sum_{i=1}^{n_j} (\overline{y_{.j}} - \overline{y_{..}})^2 = \sum_{j=1}^{g} n_j (\overline{y_{.j}} - \overline{y_{..}})^2 \quad (3.4)$$

For all g groups the total within-group sum of squares is given by:

$$SSW = \sum_{j=1}^{g} \sum_{i=1}^{n_j} (y_{ij} - \overline{y_{.j}})^2 \quad (3.5)$$

It is easily demonstrated that

$$SST = SSA + SSW$$

Estimation of σ^2

Under the assumption of homogeneity of variance the best unbiased estimator is given by:

$$s_1^{\,2} = \frac{SSA}{(g-1)}$$

$$s_2^2 = \frac{SSW}{n-g}$$

We apply the F statistic:

$$F = \frac{s_1^2}{s_2^2} \quad (3.6)$$

The F statistic has Fisher's distribution with (g-1) and (n-g) degrees of freedom.

Hypothesis

$H_0 = \mu_1 = \mu_2 = ... = \mu_g$

H_1**:** not all μ_g are equal.

Order to except or reject H_0 calculate the corresponding critical region at using α as the level of significance and then compare to our F statistic from (3.6). If the value form the test statistic falls in the critical region reject H_0, otherwise do not reject H_0.

3.1.2 Group Effects Models

An alternative model that is commonly used is the group effects model given by:

$$y_{ij} = \mu + \alpha_j + \varepsilon_{ij} \qquad i = 1, 2, ..., n \qquad j = 1, 2, ..., g \quad (3.7)$$

Where

$\sum_{j=1}^{g} \alpha_j = 0$, and the $\varepsilon_{ij} \in N(0, \sigma^2)$.

The grand mean or overall mean is μ , μ_j is equivalent to

$(\mu+\alpha_j)$, $j=1,2,....,n$ where μ is the grand mean or overall mean, $\mu=\sum_{j=1}^{g}\frac{\mu+\alpha_j}{g}$.

A test of $H_0=\mu_1=\mu_2=...=\mu_g$ is therefore equivalent to a test of $H_0=\alpha_1=\alpha_2=...=\alpha_g$. The minimum variance unbiased estimators of the parameters μ and α_j

J=1, 2….g are given by $\overline{y_{..}}$ and $(\overline{y_{.j}}-\overline{y_{..}})$, j=1,2,…..,g respectively.

3.1.3 Multiple comparisons

If the null hypothesis H_0 of equal means is rejected, a follow- up questions would be" which groups have different means?" Procedures for the comparison of cell means are called multiple comparison procedures. This section summarizes a variety of procedures commonly used to compare means.

LSD(Least Significant Difference) method

For any two groups j and l a 100(1-α)% confidence interval for $(\mu_j-\mu_l)$ may be constructed using a t distribution. A 100(1-α)% confidence interval for $(\mu_j-\mu_l)$ is given by:

$$(\overline{y_{.j}}-\overline{y_{.l}})\pm t_{\alpha/2;(n-g)^8}\left[\frac{1}{n_j}+\frac{1}{n_l}\right]^{1/2}$$

Where $s^2=\frac{SSW}{(n-g)}$. If the interval includes 0 the means are said to be not significantly different at the α level.

This procedure is commonly called the least significant difference or the LSD procedure.
The problem with multiple comparisons such as LSD is that if the numbers of groups g, is large there are a total of $g\frac{g-1}{2}$ such comparisons. If a 5% type I error probability is used, we can expect $(0.05)g\frac{g-1}{2}$ differences to appear significant even if there aren't any real differences. The type I error α in this case is the per comparison error but not the experimentwise error.
The experimentwise type I error rate refers to the probability of finding at least one significant difference over the complete set of all comparisons.

Sheffe

The most conservative approach to judging differences among means employs a result established by Scheffe(1959). For a paired comparison among means μ_j and μ_l a $100(1-\alpha)\%$ confidence interval is given by

$$(\overline{y_{.j}} - \overline{y_{.l}}) \pm s\left[(g-1)F_{\alpha;(g-1)(n-g)}\left[\frac{1}{n_j}+\frac{1}{n_l}\right]\right]^{\frac{1}{2}}$$

This method guarantees that the experimenwise error rate is controlled at level α for all possible paired comparisons among means.

Bonferroni

An approximate procedure for controlling the experimentwise error rate at α .In the case of the g means there are total of $g\frac{g-1}{2} = p$ different pairs to be compared. Letting A_J $j = 1, 2, \ldots . p$ denote the event that the j-th pair of means are declared equal we may write the probability that all p pairs are declared equal as $P[A_1, A_2 \ldots A_p]$.For an

experimentwise rate of α we would like to have $(1-\alpha) = P[A_1, A_2, ...A_p]$.By the Bonferroni inequality:

$$P[A_1, A_2.....A_p] \geq 1 - \sum_{j=1}^{p} P(\overline{A_J})$$

If we assume that $P(\overline{A_j}) = \alpha^0$ is constant for $j = 1, 2, ..., p$,

We have $(1-\alpha) \geq 1 - p\alpha^0$ and hence $\alpha^0 \geq \frac{\alpha}{p}$ or $\alpha \leq p\alpha_0$. For a given α ,the Bonferroni approach uses $\alpha^0 = \frac{\alpha}{g(g-1)/2}$,

And therefore uses $t_{\frac{\alpha^0}{2;(n-g)}}$ as the critical value of the test statistics rather than $t_{\frac{\alpha}{2;(n-g)}}$ as in the case of LSD procedure.

The Bonferroni procedure is useful for making pairwise comparisons when the F-test of equality of means did not reject the equality hypothesis.

3.2 Two- way analysis of Variance

The relationship between a quantitative variable Y and a qualitative variable X was studied using one-way analysis of variance. In this sections a second qualitative variable say Z is introduced. The categories of the two qualitative variables jointly define a set of cells and the variation of in these cell means for the variable Y is to be studied.

3.2.1 The Randomized Block Design Model

The most commonly used model for the randomized block design is given by

$$y_{ij} = \mu + \beta_i + \alpha_j + \varepsilon_{ij} \qquad i = \overline{1, b} \qquad j = \overline{1, g}$$

Where

$$\sum_{j=1}^{g} \alpha_j = 0 \qquad \sum_{i=1}^{b} \beta_j = 0$$

And the ε_{ij} are independent and identically distributed ,

$N(0,\sigma^2)$. The best linear unbiased estimators of μ_i, β_i and α_j are given by

$\hat{\mu} = \bar{y}_{..}$, $\hat{\beta}_i = \overline{y_{i.}} - \overline{y_{..}}$ and $\hat{\alpha}_j = \overline{y_{.j}} - \overline{y_{..}}$

Where

$$\overline{y_{..}} = \frac{1}{bg}\sum_{i=1}^{b}\sum_{j=1}^{g} y_{ij}\ , \qquad \overline{y_{.j}} = \frac{1}{b}\sum_{i=1}^{b} y_{ij} \qquad \overline{y_{i.}} = \frac{1}{g}\sum_{j=1}^{g} y_{ij}$$

Sums of squires

$$SST = \sum_{i=1}^{b}\sum_{j=1}^{g}(y_{ij} - \overline{y_{..}})^2 = \sum_{i=1}^{b}\sum_{j=1}^{g} y_{ij}^{\ 2} - gb\overline{y_{..}}^{2} \qquad \textbf{(3.12)}$$

$$SSA = b\sum_{j=1}^{g}(\overline{y_{.j}} - \overline{y_{..}})^2 = b\sum_{j=1}^{g}\overline{y_{.j}}^{\ 2} - gb\overline{y}_{..}^{\ 2} \qquad \textbf{(3.13)}$$

$$SSB = g\sum_{j=1}^{b}(\overline{y_{i.}} - \overline{y_{..}})^2 = g\sum_{i=1}^{b}\overline{y_{i.}}^{\ 2} - gb\overline{y_{..}}^{2} \qquad \textbf{(3.14)}$$

$$SSE = SST - SSA - SSB$$

$$SSE = \sum_{i=1}^{b}\sum_{j=1}^{g}(y_{ij} - \overline{y_{.j}} - \overline{y_{i.}} + \overline{y_{..}})^2 = \sum_{i=1}^{b}\ \sum_{j=1}^{g} y_{ij}^{\ 2} - b\sum_{j=1}^{g}\overline{y_{.j}}^{2} - g\sum_{i=1}^{b}\overline{y_{i.}}^{2} + gb\overline{y}^{2}$$

3.2.2 The Two Factor Factorial

If the relationship between a dependent quantitative variable Y and two qualitative variables is of interest then a two factor model is required. We assume that the first factor X has g levels while the second factor Z has b levels. The cross classifications of the two factors therefore has bg cells.We shall assume that c observations are randomly selected from each of the bg cells yielding a total of n=bgc observations.

Alternatively, a total of n experimental units are randomly assigned to the bg treatment combinations, in such a way that each combination is observed on c occasions.

The balanced two-way model is usually given by:

$$y_{ijh} = \mu + \alpha_j + \beta_j + (\alpha\beta)_{ij} + \varepsilon_{ijh}, \quad i = \overline{1,b}\,;\ j = \overline{1,g}\,;\ h = \overline{1,c}$$

Where

$$\sum_{i=1}^{b} \beta_j = \sum_{j=1}^{g} \alpha_j = \sum_{i=1}^{b} (\alpha\beta)_{ij} = \sum_{j=1}^{g} (\alpha\beta)_{ij} = 0$$

And the ε_{ijh} are mutually independent $N(0,\sigma^2)$.

The parameters $(\alpha\beta)_{ij}$ are called interaction parameters.

The best linear unbiased estimators of the parameters are given by

$$\hat{\alpha}_j = \overline{y}_{.j.} - \overline{y}_{...}$$

$$\hat{\beta}_i = \overline{y}_{i..} - \overline{y}_{...}$$

$$\hat{\mu}_{ij} = \overline{y}_{ij.}$$

And

$$(\hat{\alpha}\hat{\beta})_{ij} = \left(\overline{y}_{ij.} - \overline{y}_{i..} - \overline{y}_{.j.} + \overline{y}_{...}\right) = \left[\overline{y}_{ij} - (\overline{y}_{i..} - \overline{y}_{...}) - (\overline{y}_{.j.} - \overline{y}_{...}) - \overline{y}_{...}\right]$$ For the balanced two-way design three independent hypothesis tests can be carried out using an F- statistic.

The hypotheses are :

$$H_{01} : \beta_1 = \beta_2 = ... = \beta_g = 0$$

$$H_{02} : \alpha_1 = \alpha_2 = ... = \alpha_b = 0$$

$$H_{03} : (\alpha\beta)_{11} = (\alpha\beta)_{12} = ... = (\alpha\beta)_{bg} = 0$$

The sum of squares are given by:

$$SST = \sum_{i=1}^{b} \sum_{j=1}^{g} \sum_{h=1}^{c} \left(y_{ijh} - \bar{y}_{...} \right)^2 = \sum_{i=1}^{b} \sum_{j=1}^{g} \sum_{h=1}^{c} y^2_{ijh} - bgc\bar{y}^2_{...}$$

$$SSA = bc\sum_{j=1}^{g} \left(\bar{y}_{.j.} - \bar{y}_{...} \right)^2 = bc\sum_{j=1}^{g} \bar{y}^2_{.j.} - bgc\bar{y}^2_{...}$$

$$SSB = gc\sum_{i=1}^{b} \left(\bar{y}_{i..} - \bar{y}_{...} \right)^2 = gc\sum_{i=1}^{b} \bar{y}^2_{.j.} - bgc\bar{y}^2_{...}$$

$$SSI = c\sum_{i=1}^{b} \sum_{j=1}^{g} \left(\bar{y}_{ij.} - \bar{y}_{i..} - \bar{y}_{.j.} + \bar{y}_{...} \right)^2 = c\sum_{i=1}^{b}\sum_{j=1}^{g} \bar{y}^2_{ij.} - bc\sum_{j=1}^{g} \bar{y}^2_{.j.} - gc\sum_{i=1}^{b} \bar{y}^2_{i..} + bgc\bar{y}^2_{...}$$

$$SSE = \sum_{i=1}^{b}\sum_{j=1}^{g}\sum_{h=1}^{c} \left(y_{ijh} - \bar{y}_{ij.} \right)^2 = \sum_{i=1}^{b}\sum_{j=1}^{g}\sum_{h=1}^{c} y^2_{ijh} - c\sum_{i=1}^{b}\sum_{j=1}^{g} \bar{y}^2_{ij.}$$

4. **Statistical Analysis of the Effects of Two Medicaments**

In this chapter we will examine the effects of two medicaments Tiamulin – produced by “Novartis” pharmaceutical company and Tiamulin – produced by “Balcanpharm” pharmaceutical company on an experimental population. The research teams have treated the animals with these two medicaments and one control which is called placebo.We have three types of symptoms: diarrhoea,dehydration,appetite.The data are grouped in one table called -major matrix of data.

Description of the data matrices

Main Data Matrix

The main matrix of data consists of 10 columns:

The first column is named:Type.This column contains three types of symptoms studied: diarrhoea,dehydration,appetite.

The second column is named:Weight.This column contains a number of objects excibiting certain symptoms.

The third column is named:Tiamulin.It contains the two medicaments and the control product.

Day1,Day2,……Day7 consists levels of a symptom of the day.

Secondary Data Matrices

To obtain secondary data matrices are removed columns and rows that do not participate in a particular analysis.

In conducting an analysis of the impact of drugs on dehydration symptom data were deleted two other symptoms that are irrelevant to this analysis.

4.1 Analysis of active medicaments with including placebo

4.1.1 Impact and comparison of medicaments according to the symptom “Diarrhea”.

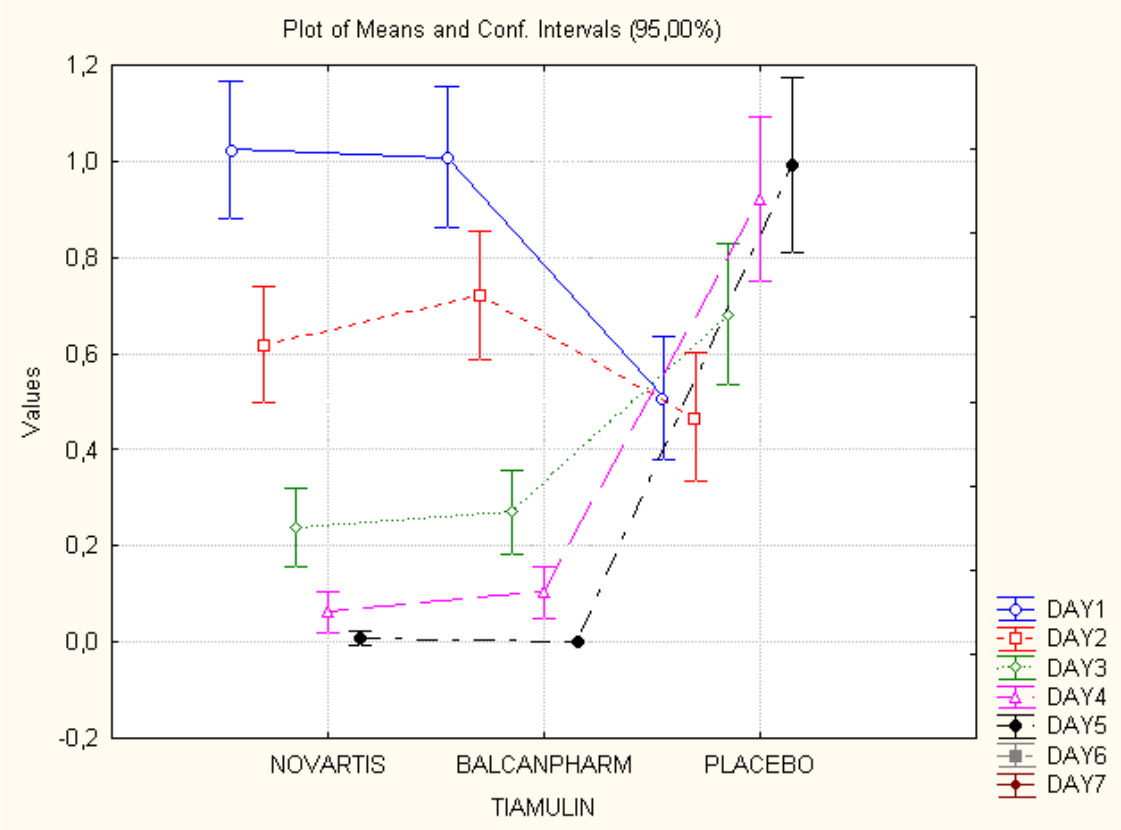


Figure 4.1: **Effect of medicaments Tiamulin on the symptom “Diarrhea”.**

This figure reflected the impact of two medicaments Tiamulin produced by “Novartis” and Tiamulin –“Balcanpharm” on the symptom “Diarrhea”during different days of the treatment.We found that the impact of factor Tiamulin has a statistically significant effect.The level of agreement (p-level) is less than 0.0001.In this case it has a probability to

make a mistake, when we accept the hypothesis that factor effects the response,but this is not so.

During the first day of the treatment,the effect of Tiamulin- Novartis is slightly greater than that of other medicament.During the second day the impact of the medicament Tiamulin-Balcanpharma is more strong.

It is mentioned after the third day but with less force.

We can see these features in the following table: We use The Method of Sheffe to see whether the effects of both medicaments is equal to the control group and in which days is the same impact.We see the results on the five tables.

During the second day we see that the difference between the impact of the medicaments “Novartis” and ”Balcanpharm”is not statistically significant.We can see demonstrated equivalence for the first,third,fourth and fifth day.

Testing equivalence:

	Breakdown Table of Descriptive Statistics (Diariq_Tiamulin-Placebo.sta) N=378 (No missing data in dep. var. list)					
	Tiamulin /Days	Day 1 Means	Day 2 Means	Day 3 Means	Day 4 Means	Day 5 Means
	Novartis	1,023810	0,619048	0,238095	0,063492	0,007937
	Balcanpharm	1,007937	0,722222	0,269841	0,103175	0,000000
	Placebo	0,507937	0,468254	0,682540	0,920635	0,992063

Fist Day:

	Scheffe Test; Variable: DAY1 (DATAdia.STA) Marked differences are significant at p < ,05000		
TIAMULIN	{1} M=1,0238	{2} M=1,0079	{3} M=,50794
Novartis {1}		0,987438	0,000002
Balcanpharm{2}	0,987438		0,000005
Placebo {3}	0,000002	0,000005	

Second Day:

TIAMULIN	Scheffe Test; Variable: DAY2 (DATAdia.STA) Marked differences are significant at p < ,0500		
	{1} M=,61905	{2} M=,72222	{3} M=,46825
Novartis {1}		0,534445	0,262951
Balcanpharm {2}	0,534445		0,023178
Placebo {3}	0,262951	0,023178	

Third Day:

TIAMULIN	Scheffe Test; Variable: DAY3 (DATAdia.STA) Marked differences are significant at p < ,05000		
	{1} M=,23810	{2} M=,26984	{3} M=,68254
Novartis {1}		0,920130	0,000000
Balcanpharm{2}	0,920130		0,000001
Placebo {3}	0,000000	0,000001	

Fourth Day:

TIAMULIN	Scheffe Test; Variable: DAY4 (DATAdia.STA) Marked differences are significant at p < ,0500		
	{1} M=,06349	{2} M=,10317	{3} M=,92063
Novartis {1}		0,872524	0,000000
Balcanpharm {2}	0,872524		0,000000
Placebo {3}	0,000000	0,000000	

Fifth Day:

TIAMULIN	Scheffe Test; Variable: DAY5 (DATAdia.STA) Marked differences are significant at p < ,05000		
	{1} M=,00794	{2} M=0,0000	{3} M=,99206
Novartis{1}		0,994379	0,00
Balcanpharm{2}	0,994379		0,00
Placebo {3}	0,000000	0,000000	

4.1.2 Impact and comparison of medicaments according to the symptom “Dehydration”.

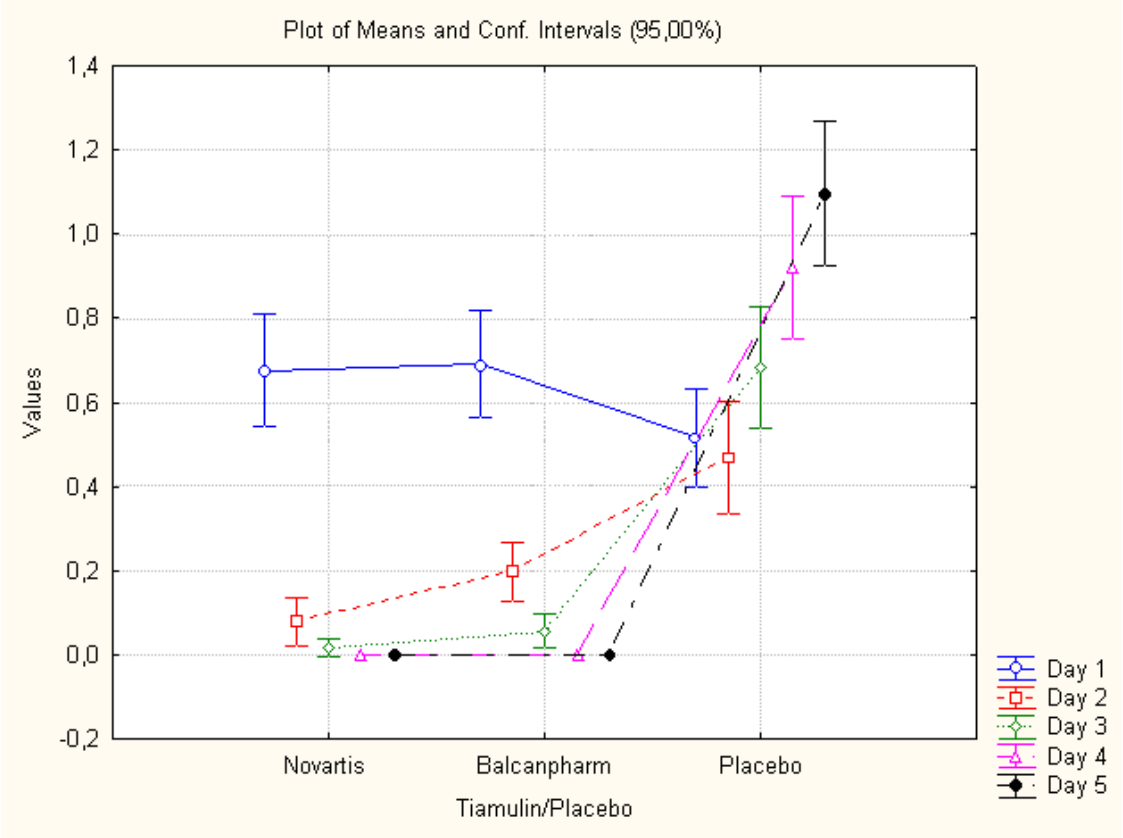


Figure 4.2: **Effect of medicaments Tiamulin on the symptom “Dehydration”.**

This figure reflected the impact of two medicaments Tiamulin produced by “Novartis” and Tiamulin –“Balcanpharm” on the symptom “Dehydration”during different days of the treatment. We found that the impact of factor Tiamulin has a statistically significant effect.The level of agreement (p-level) is less than 0.0001.We see that the antibiotic Tiamulin-“Balcanpharm” has a predominantly effect during the first three days and it is more noticeable in the second.On the fourth day the symptom no longer occurs. We can see these features in the following table:

Testing equivalence

We use again the method of Scheffe.The results are presented in tables 4.8-4.11.

During the first day we noticed that differences in impact between the medicaments and controller product are not statistically significant.We can see that there is a equivalence between the two medicaments .For the second day we can say that there is not equivalence between the two drugs and there is not statistically significant difference.For the past three days the effects of both two medicaments is equivalent.

Effect	Multivariate Tests of Significance (Dehidrataciq_Tiamulin-Placebo.st Sigma-restricted parameterization Effective hypothesis decomposition					
	Test	Value	F	Effect df	Error df	p
Intercept	Wilks	0,482603	79,54942	5	371	0,00
Tiamulin/Placebo	Wilks	0,437595	37,96766	10	742	0,00

First Day:

TIAMULIN	Scheffe Test; Variable: DAY1 (DATAdehi.STA) Marked differences are significant at p < ,05000		
	{1} M=,67460	{2} M=,69048	{3} M=,51587
Novartis {1}		0,984624	0,213679
Balcanpharm{2}	0,984624		0,154778
Placebo {3}	0,213679	0,154778	

Second Day:

TIAMULIN	Scheffe Test; Variable: DAY2 (DATAdehi.STA) Marked differences are significant at p < ,0500		
	{1} M=,07937	{2} M=,19841	{3} M=,46825
Novartis {1}		0,203233	0,000000
Balcanpharm {2}	0,203233		0,000320
Placebo {3}	0,000000	0,000320	

Third Day:

TIAMULIN	{1} M=,01587	{2} M=,05556	{3} M=,68254
Novartis {1}		0,820344	0,000000
Balcanpharm {2}	0,820344		0,000000
Placebo {3}	0,000000	0,000000	

Scheffe Test; Variable: DAY3 (DATAdehi.STA)
Marked differences are significant at p < ,05000

Fourth Day:

TIAMULIN	{1} M=0,0000	{2} M=0,0000	{3} M=,92063
Novartis {1}		1,000000	0,00
Balcanpharm {2}	1,000000		0,00
Placebo {3}	0,000000	0,000000	

Scheffe Test; Variable: DAY4 (DATAdehi.STA)
Marked differences are significant at p < ,05000

Fifth Day:

TIAMULIN	{1} M=0,0000	{2} M=0,0000	{3} M=1,0952
Novartis{1}		1,000000	0,00
Balcanpharm {2}	1,000000		0,00
Placebo {3}	0,000000	0,000000	

Scheffe Test; Variable: DAY5 (DATAdehi.STA)
Marked differences are significant at p < ,0500

4.1.3 Impact and comparison of medicaments according to the symptom “Apetite”.

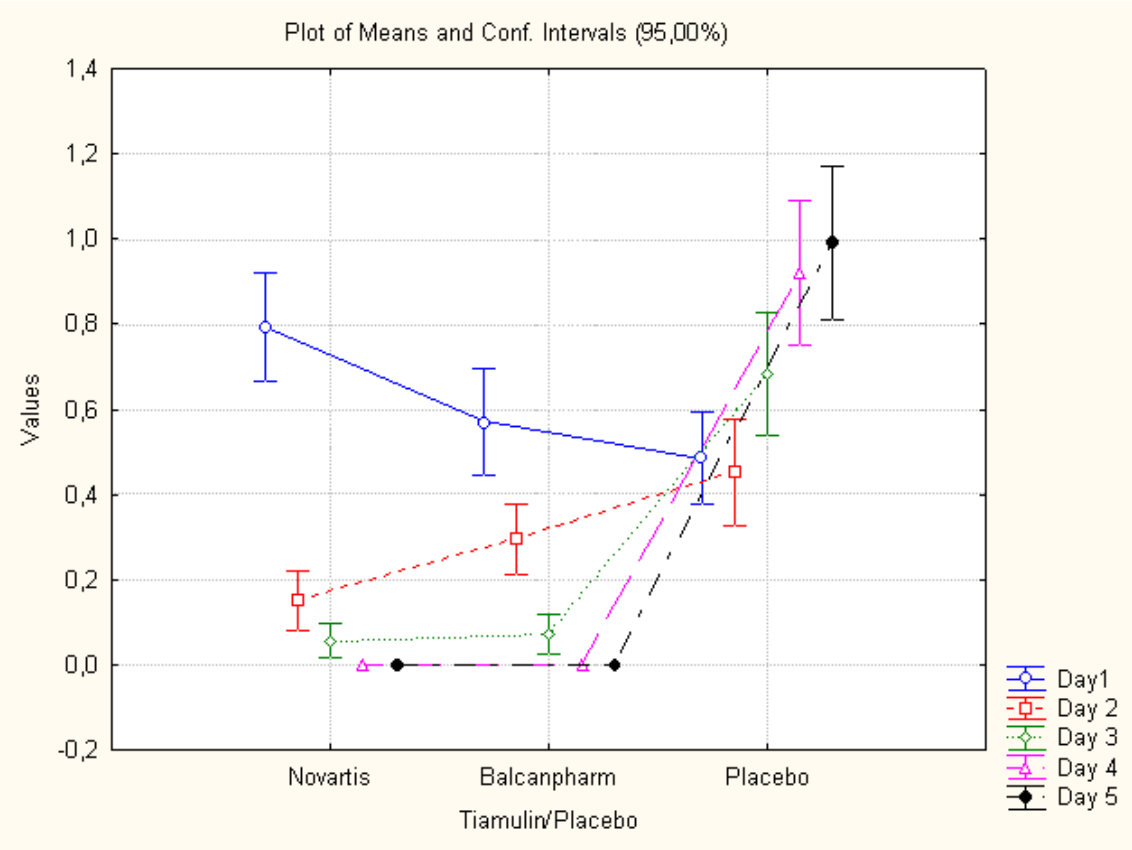


Figure 4.2: **Effect of medicaments Tiamulin on the symptom “Apetite”.**

We found that the impact of factor Tiamulin has a statistically significant effect.The level of agreement (p-level) or significance probability is less than 0.0001.During the first day the effect of the antibiotic “Tiamulin-Novartis” is strong.During the second day the effect of the

antibiotic “Tiamulin-Balcanpharm” is much stronger.And during the following days of the treatment there is almost no difference. We can see these features in the following tables:

Effect	Multivariate Tests of Significance (Apetit_Tiamulin-Placebo.sta Sigma-restricted parameterization Effective hypothesis decomposition					
	Test	Value	F	Effect df	Error df	p
Intercept	Wilks	0,511770	70,78698	5	371	0,00
Tiamulin/Placebo	Wilks	0,454405	35,87343	10	742	0,00

Testing equivalence:

We use again the method of Scheffe.The results are presented in tables 4.13 -4.16.During the first day there is a statistically significant difference in the effect of both drugs.For the second day we can say that there is no statistically significant difference but the equivalence is weak.For the other days the impact of both drugs is equivalent.

	Breakdown Table of Descriptive Statistics (Apetit_Tiamulin-Placebo.sta) N=378 (No missing data in dep. var. list)					
	Тиамулин/Плацебо	Day 1 Means	Day 2 Means	Day 3 Means	Day 4 Means	Day 5 Means
	Novartis	0,793651	0,150794	0,055556	0,000000	0,000000
	Balcanpharm	0,571429	0,293651	0,071429	0,000000	0,000000
	Placebo	0,484127	0,452381	0,682540	0,920635	0,992063

First Day:

Tiamulin/Placebo	Scheffe Test; Variable: Day1 (Apetit_Tiamulin-Placebo.sta) Marked differences are significant at p < ,05000		
	{1} M=,79365	{2} M=,57143	{3} M=,48413
Novartis {1}		0,036707	0,001731
Balcanpharm {2}	0,036707		0,598178
Placebo {3}	0,001731	0,598178	

Second Day:

	Scheffe Test; Variable: Day 2 (Apetit_Tiamulin-Placebo2.sta) Marked differences are significant at p < ,05000		
Tiamulin/Placebo	{1} M=,15079	{2} M=,29365	{3} M=,45238
Novartis {1}		0,116483	0,000083
Balcanpharm {2}	0,116483		0,070596
Placebo {3}	0,000083	0,070596	

Third Day:

	Scheffe Test; Variable: Day 3 (Apetit_Tiamulin-Placebo2.sta) Marked differences are significant at p < ,05000		
Tiamulin/Placebo	{1} M=,05556	{2} M=,07143	{3} M=,68254
Novartis {1}		0,970757	0,000000
Balcanpharm {2}	0,970757		0,000000
Placebo {3}	0,000000	0,000000	

Fourth and Fifth Day:

	Scheffe Test; Variable: Day 4 (Apetit_Tiamulin-Placebo2.sta) Marked differences are significant at p < ,05000		
Tiamulin/Placebo	{1} M=0,0000	{2} M=0,0000	{3} M=,92063
Novartis {1}		1,000000	0,00
Balcanpharm {2}	1,000000		0,00
Placebo {3}	0,000000	0,000000	

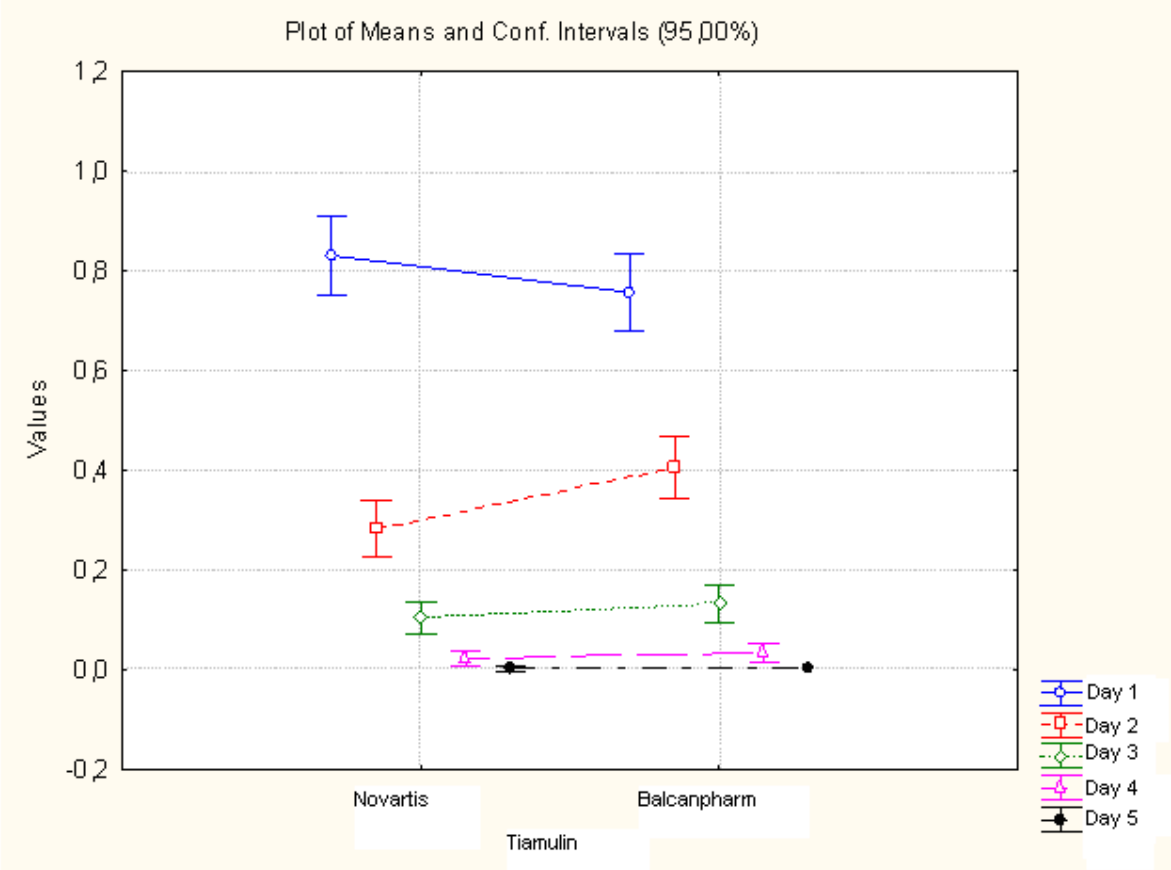
4.2 Analysis of the two medicaments without including placebo

The Impact of the two medicaments:

Here we are interested in the effects of Tiamulin factor and differences in the effects of both drugs on the three symptoms together.

We can see the results in these tables.

We notice that the main differences are in the first and second day after application of medicaments.



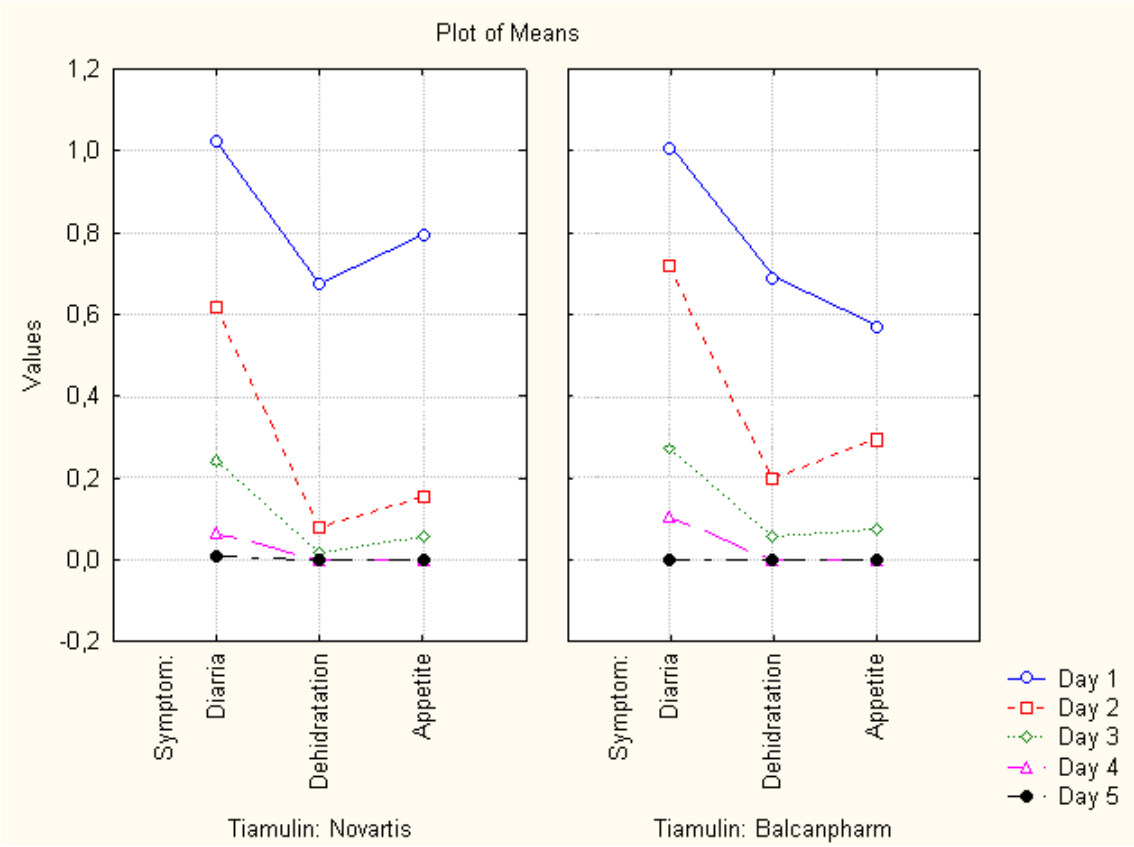
Testing equivalence:

To follow exactly in which symptoms and in which days are the differences we use a method of Sheffe.We can see this on table 4.19.Statistically significant symptoms on the second day are “dehydratation” on the second day and “appetite” on the first and second day after taking the medicaments.

	Breakdown Table of Descriptive Statistics (Diariq-Dehidrataciq-Apetit_Tiamulin.st N=756 (No missing data in dep. var. list)					
	Tiamulin	Day 1 Means	Day 2 Means	Day 3 Means	Day 4 Means	Day 5 Means
	Novartis	0,830688	0,283069	0,103175	0,021164	0,002646
	Balcanpharm	0,756614	0,404762	0,132275	0,034392	0,000000
	All Grps	0,793651	0,343915	0,117725	0,027778	0,001323

Guideline of both medicaments effects on the three symptoms

Figure 4.5:Effects of both medicines on the three symptoms.



We use the two-factor analysis of variance where the two factors are “Symptom” and “Tiamulin”.We can see this on the table 4.17.

There is no statistically significant effect (A*B).

The effect of the two medicaments on the three symptoms is the same.

Effect	Multivariate Tests of Significance (Diariq-Dehidrataciq-Apetit_TiamulinSPlac.sta) Sigma-restricted parameterization Effective hypothesis decomposition					
	Test	Value	F	Effect df	Error df	p
Symptom (A)	Wilks	0,819886	15,5753	10	1492	0,000000
Tiamulin (B)	Wilks	0,961786	5,9281	5	746	0,000022
Symptom*Tiamulin	Wilks	0,980253	1,4953	10	1492	0,135069

4.3 Summaries of the results

Analysis of the medicaments with including a placebo:

1.The influence of the two medicaments-Tiamulin –"Novartis" and Tiamulin-"Balcanpharm" is statistically significant.
2.The impact of both two drugs is equivalent in the last three days of the therapy.
3.There are differences in symptoms on the second day and statistically significant difference.

Analysis of the medicaments without placebo:

1.There is statistically significant difference on the symptoms "Dehydration" on the second day and "Appetite" on the first and second day.
2.The effects of the active medicaments is similar.

Chapter 5

Conclusion

This final project introduced us the concrete application of analysis of variance-assesing the effect of two drugs-“Tiamulin”-Novartis and
“Tiamulin”-Balcanpharm.We used the method of Sheffe to see their similarities and differences in their impact.

We acquainted with the basic European rules and standards which must be respected.

The final project could be developed in different directions –to determine the maximum and minimum optimal dose of the medication,to check for any side effects of the medicaments,to determine what combinations are beneficial and t.e.

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Contents

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
1	DIA	1,000	NOVARTIS	3,000	2,000	2,000	1,000	0,000		
2	DIA	2,000	NOVARTIS	2,000	1,000	1,000	0,000	0,000		
3	DIA	3,000	NOVARTIS	2,000	1,000	0,000	0,000	0,000		
4	DIA	4,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
5	DIA	5,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
6	DIA	6,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
7	DIA	1,000	NOVARTIS	1,000	1,000	1,000	1,000	0,000		
8	DIA	2,000	NOVARTIS	1,000	1,000	1,000	0,000	0,000		
9	DIA	3,000	NOVARTIS	1,000	2,000	1,000	0,000	0,000		
10	DIA	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
11	DIA	5,000	NOVARTIS	2,000	0,000	0,000	0,000	0,000		
12	DIA	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
13	DIA	1,000	NOVARTIS	2,000	1,000	1,000	0,000	0,000		
14	DIA	2,000	NOVARTIS	2,000	1,000	1,000	0,000	0,000		
15	DIA	3,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
16	DIA	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
17	DIA	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
18	DIA	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
19	DIA	1,000	NOVARTIS	3,000	2,000	2,000	1,000	1,000		
20	DIA	2,000	NOVARTIS	3,000	2,000	1,000	1,000	0,000		
21	DIA	3,000	NOVARTIS	2,000	2,000	1,000	1,000	0,000		
22	DIA	4,000	NOVARTIS	1,000	1,000	1,000	0,000	0,000		
23	DIA	5,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
24	DIA	6,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
25	DIA	1,000	NOVARTIS	3,000	1,000	1,000	0,000	0,000		
26	DIA	2,000	NOVARTIS	1,000	1,000	1,000	0,000	0,000		
27	DIA	3,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
28	DIA	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
29	DIA	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
30	DIA	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
31	DIA	1,000	NOVARTIS	3,000	1,000	1,000	0,000	0,000		
32	DIA	2,000	NOVARTIS	1,000	1,000	1,000	0,000	0,000		
33	DIA	3,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
34	DIA	4,000	NOVARTIS	2,000	2,000	0,000	0,000	0,000		
35	DIA	5,000	NOVARTIS	2,000	0,000	0,000	0,000	0,000		
36	DIA	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
37	DEHI	1,000	NOVARTIS	3,000	0,000	0,000	0,000	0,000		
38	DEHI	2,000	NOVARTIS	2,000	0,000	0,000	0,000	0,000		
39	DEHI	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
40	DEHI	4,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
41	DEHI	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
42	DEHI	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
43	DEHI	1,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
44	DEHI	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
45	DEHI	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
46	DEHI	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
47	DEHI	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
48	DEHI	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
49	DEHI	1,000	NOVARTIS	2,000	1,000	0,000	0,000	0,000		
50	DEHI	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
51	DEHI	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
52	DEHI	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
53	DEHI	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
54	DEHI	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
55	DEHI	1,000	NOVARTIS	3,000	1,000	1,000	0,000	0,000		
56	DEHI	2,000	NOVARTIS	3,000	2,000	0,000	0,000	0,000		
57	DEHI	3,000	NOVARTIS	2,000	1,000	0,000	0,000	0,000		
58	DEHI	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
59	DEHI	5,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
60	DEHI	6,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
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62	DEHI	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
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64	DEHI	4,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
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66	DEHI	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
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70	DEHI	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
71	DEHI	5,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
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76	APPE	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
77	APPE	5,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
78	APPE	6,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
79	APPE	1,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
80	APPE	2,000	NOVARTIS	1,000	1,000	0,000	0,000	0,000		
81	APPE	3,000	NOVARTIS	1,000	0,000	1,000	0,000	0,000		
82	APPE	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
83	APPE	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
84	APPE	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
85	APPE	1,000	NOVARTIS	2,000	1,000	0,000	0,000	0,000		
86	APPE	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
87	APPE	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
88	APPE	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
89	APPE	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
90	APPE	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
91	APPE	1,000	NOVARTIS	3,000	1,000	1,000	0,000	0,000		
92	APPE	2,000	NOVARTIS	3,000	2,000	0,000	0,000	0,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
93	APPE	3,000	NOVARTIS	2,000	1,000	0,000	0,000	0,000		
94	APPE	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
95	APPE	5,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
96	APPE	6,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
97	APPE	1,000	NOVARTIS	2,000	0,000	0,000	0,000	0,000		
98	APPE	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
99	APPE	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
100	APPE	4,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
101	APPE	5,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
102	APPE	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
103	APPE	1,000	NOVARTIS	3,000	1,000	1,000	0,000	0,000		
104	APPE	2,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
105	APPE	3,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
106	APPE	4,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
107	APPE	5,000	NOVARTIS	1,000	0,000	0,000	0,000	0,000		
108	APPE	6,000	NOVARTIS	0,000	0,000	0,000	0,000	0,000		
109	DIA	1,000	BALCANPHARM	3,000	3,000	2,000	1,000	0,000		
110	DIA	2,000	BALCANPHARM	3,000	2,000	2,000	0,000	0,000		
111	DIA	3,000	BALCANPHARM	2,000	2,000	1,000	0,000	0,000		
112	DIA	4,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
113	DIA	5,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
114	DIA	6,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
115	DIA	1,000	BALCANPHARM	1,000	1,000	1,000	1,000	0,000		
116	DIA	2,000	BALCANPHARM	1,000	1,000	1,000	1,000	0,000		
117	DIA	3,000	BALCANPHARM	1,000	2,000	1,000	1,000	0,000		
118	DIA	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
119	DIA	5,000	BALCANPHARM	2,000	0,000	0,000	0,000	0,000		
120	DIA	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
121	DIA	1,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
122	DIA	2,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
123	DIA	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
124	DIA	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
125	DIA	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
126	DIA	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
127	DIA	1,000	BALCANPHARM	3,000	3,000	1,000	1,000	0,000		
128	DIA	2,000	BALCANPHARM	3,000	2,000	1,000	1,000	0,000		
129	DIA	3,000	BALCANPHARM	3,000	2,000	1,000	1,000	0,000		
130	DIA	4,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
131	DIA	5,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
132	DIA	6,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
133	DIA	1,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
134	DIA	2,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
135	DIA	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
136	DIA	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
137	DIA	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
138	DIA	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
139	DIA	1,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
140	DIA	2,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
141	DIA	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
142	DIA	4,000	BALCANPHARM	2,000	2,000	0,000	0,000	0,000		
143	DIA	5,000	BALCANPHARM	2,000	0,000	0,000	0,000	0,000		
144	DIA	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
145	DEHI	1,000	BALCANPHARM	3,000	1,000	1,000	0,000	0,000		
146	DEHI	2,000	BALCANPHARM	2,000	1,000	0,000	0,000	0,000		
147	DEHI	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
148	DEHI	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
149	DEHI	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
150	DEHI	6,000	BALCANPHARM	0,000	0,000	1,000	0,000	0,000		
151	DEHI	1,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
152	DEHI	2,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
153	DEHI	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
154	DEHI	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
155	DEHI	5,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
156	DEHI	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
157	DEHI	1,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
158	DEHI	2,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
159	DEHI	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
160	DEHI	4,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
161	DEHI	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
162	DEHI	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
163	DEHI	1,000	BALCANPHARM	3,000	1,000	0,000	0,000	0,000		
164	DEHI	2,000	BALCANPHARM	2,000	0,000	0,000	0,000	0,000		
165	DEHI	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
166	DEHI	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
167	DEHI	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
168	DEHI	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
169	DEHI	1,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
170	DEHI	2,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
171	DEHI	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
172	DEHI	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
173	DEHI	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
174	DEHI	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
175	DEHI	1,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
176	DEHI	2,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
177	DEHI	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
178	DEHI	4,000	BALCANPHARM	2,000	1,000	0,000	0,000	0,000		
179	DEHI	5,000	BALCANPHARM	2,000	1,000	0,000	0,000	0,000		
180	DEHI	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
181	APPE	1,000	BALCANPHARM	3,000	2,000	1,000	0,000	0,000		
182	APPE	2,000	BALCANPHARM	2,000	1,000	1,000	0,000	0,000		
183	APPE	3,000	BALCANPHARM	2,000	1,000	0,000	0,000	0,000		
184	APPE	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
185	APPE	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
186	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
187	APPE	1,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
188	APPE	2,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
189	APPE	3,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
190	APPE	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
191	APPE	5,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
192	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
193	APPE	1,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
194	APPE	2,000	BALCANPHARM	1,000	1,000	1,000	0,000	0,000		
195	APPE	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
196	APPE	4,000	BALCANPHARM	1,000	0,000	0,000	0,000	0,000		
197	APPE	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
198	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
199	APPE	1,000	BALCANPHARM	3,000	1,000	0,000	0,000	0,000		
200	APPE	2,000	BALCANPHARM	2,000	1,000	1,000	0,000	0,000		
201	APPE	3,000	BALCANPHARM	2,000	1,000	0,000	0,000	0,000		
202	APPE	4,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
203	APPE	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
204	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
205	APPE	1,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
206	APPE	2,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
207	APPE	3,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
208	APPE	4,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
209	APPE	5,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
210	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
211	APPE	1,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
212	APPE	2,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
213	APPE	3,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
214	APPE	4,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
215	APPE	5,000	BALCANPHARM	1,000	1,000	0,000	0,000	0,000		
216	APPE	6,000	BALCANPHARM	0,000	0,000	0,000	0,000	0,000		
217	DIA	1,000	PLACEBO	3,000	3,000	3,000	9,000	9,000	9,000	9,000
218	DIA	2,000	PLACEBO	3,000	3,000	3,000	2,000	2,000	3,000	3,000
219	DIA	3,000	PLACEBO	1,000	1,000	2,000	2,000	2,000	2,000	3,000
220	DIA	4,000	PLACEBO	1,000	1,000	1,000	1,000	2,000	2,000	2,000
221	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000	1,000	1,000
222	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000	1,000	1,000
223	DIA	1,000	PLACEBO	2,000	2,000	2,000	2,000	1,000		
224	DIA	2,000	PLACEBO	2,000	2,000	1,000	2,000	2,000		
225	DIA	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
226	DIA	4,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
227	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
228	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
229	DIA	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
230	DIA	2,000	PLACEBO	2,000	2,000	1,000	2,000	2,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
231	DIA	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
232	DIA	4,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
233	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
234	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
235	DIA	1,000	PLACEBO	2,000	2,000	2,000	2,000	3,000		
236	DIA	2,000	PLACEBO	2,000	2,000	2,000	2,000	2,000		
237	DIA	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
238	DIA	4,000	PLACEBO	1,000	1,000	1,000	1,000	2,000		
239	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
240	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
241	DIA	1,000	PLACEBO	1,000	2,000	2,000	2,000	3,000		
242	DIA	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
243	DIA	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
244	DIA	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
245	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
246	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
247	DIA	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
248	DIA	2,000	PLACEBO	1,000	1,000	1,000	2,000	2,000		
249	DIA	3,000	PLACEBO	1,000	1,000	1,000	1,000	1,000		
250	DIA	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
251	DIA	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
252	DIA	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
253	DEHI	1,000	PLACEBO	3,000	3,000	3,000	9,000	9,000		
254	DEHI	2,000	PLACEBO	2,000	3,000	3,000	2,000	2,000		
255	DEHI	3,000	PLACEBO	1,000	1,000	2,000	2,000	2,000		
256	DEHI	4,000	PLACEBO	1,000	1,000	1,000	1,000	2,000		
257	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
258	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
259	DEHI	1,000	PLACEBO	2,000	2,000	2,000	2,000	2,000		
260	DEHI	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
261	DEHI	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
262	DEHI	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
263	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
264	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	1,000		
265	DEHI	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
266	DEHI	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
267	DEHI	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
268	DEHI	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
269	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
270	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	1,000		
271	DEHI	1,000	PLACEBO	2,000	2,000	2,000	2,000	3,000		
272	DEHI	2,000	PLACEBO	2,000	2,000	2,000	2,000	2,000		
273	DEHI	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
274	DEHI	4,000	PLACEBO	1,000	1,000	1,000	1,000	2,000		
275	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
276	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
277	DEHI	1,000	PLACEBO	2,000	2,000	2,000	2,000	3,000		
278	DEHI	2,000	PLACEBO	2,000	2,000	1,000	2,000	2,000		
279	DEHI	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
280	DEHI	4,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
281	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
282	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
283	DEHI	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
284	DEHI	2,000	PLACEBO	1,000	1,000	1,000	2,000	2,000		
285	DEHI	3,000	PLACEBO	1,000	1,000	1,000	1,000	1,000		
286	DEHI	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
287	DEHI	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
288	DEHI	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
289	APPE	1,000	PLACEBO	3,000	3,000	3,000	9,000	9,000		
290	APPE	2,000	PLACEBO	2,000	2,000	3,000	2,000	2,000		
291	APPE	3,000	PLACEBO	1,000	1,000	2,000	2,000	2,000		
292	APPE	4,000	PLACEBO	0,000	1,000	1,000	1,000	2,000		
293	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
294	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
295	APPE	1,000	PLACEBO	1,000	2,000	2,000	2,000	1,000		
296	APPE	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
297	APPE	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
298	APPE	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
299	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
300	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
301	APPE	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
302	APPE	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
303	APPE	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
304	APPE	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
305	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
306	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
307	APPE	1,000	PLACEBO	2,000	2,000	2,000	2,000	3,000		
308	APPE	2,000	PLACEBO	2,000	2,000	2,000	2,000	2,000		
309	APPE	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
310	APPE	4,000	PLACEBO	1,000	1,000	1,000	1,000	2,000		
311	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
312	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
313	APPE	1,000	PLACEBO	1,000	2,000	2,000	2,000	3,000		
314	APPE	2,000	PLACEBO	1,000	2,000	1,000	2,000	2,000		
315	APPE	3,000	PLACEBO	1,000	1,000	2,000	1,000	1,000		
316	APPE	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		
317	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
318	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		
319	APPE	1,000	PLACEBO	0,000	0,000	1,000	1,000	1,000		
320	APPE	2,000	PLACEBO	1,000	1,000	1,000	2,000	2,000		
321	APPE	3,000	PLACEBO	1,000	1,000	1,000	1,000	1,000		
322	APPE	4,000	PLACEBO	1,000	0,000	1,000	1,000	1,000		

	1 TYPE	2 WEIGHT	3 TIAMULIN/PLACEBO	4 DAY1	5 DAY2	6 DAY3	7 DAY4	8 DAY5	9 DAY6	10 DAY7
323	APPE	5,000	PLACEBO	0,000	0,000	0,000	1,000	1,000		
324	APPE	6,000	PLACEBO	0,000	0,000	0,000	0,000	0,000		